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Original Article

Association of inflammation and oxidative stress with obstructive sleep apnea in ischemic stroke patients

Chung-Yao Chen [a,b,*], Chia-Ling Chen [c,d], Chung-Chieh Yu [b,e], Tai-Tzung Chen [a,b], Shih-Ting Tseng [a,b], Chien-Hui Ho [a,b]

[a] Department of Physical Medicine and Rehabilitation, Chang Gung Memorial Hospital, Keelung, Taiwan
[b] School of Medicine, College of Medicine, Chang Gung University, Taoyuan, Taiwan
[c] Department of Physical Medicine and Rehabilitation, Chang Gung Memorial Hospital, Taoyuan, Taiwan
[d] Graduate Institute of Early Intervention, College of Medicine, Chang Gung University, Taoyuan, Taiwan
[e] Division of Pulmonary, Critical Care and Sleep Medicine, Department of Internal Medicine, Chang Gung Memorial Hospital, Keelung, Taiwan

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ABSTRACT

Objective: The role of obstructive sleep apnea (OSA) in the mortality and further cardiovascular risk in subjects with ischemic stroke remains a contentious issue. Oxidative stress and inflammatory reaction due to OSA have seldom been studied in stable ischemic stroke patients.
Patients/Methods: This cross-sectional, prospective study involved 92 consecutive ischemic stroke patients who were admitted to the Rehabilitation ward. All subjects received polysomnography and laboratory tests for oxidative stress and inflammatory biomarkers, including: C-reactive protein (CRP), interleukin 6 (IL-6), total antioxidant capacity (TAC), and urinary 8-hydroxy-2-deoxyguanosine. Differences in study variables between patients with or without severe OSA were compared, and multivariate linear regression analyses were used to assess the relationship between OSA severity and target biomarkers.
Results: Participants in the severe OSA group were significantly older ($p = 0.002$), had a significantly higher risk of hypertension ($p = 0.021$) and a lower level of CRP ($p = 0.006$). Among the subjects with ischemic stroke and severe OSA, the levels of CRP, IL-6, and TAC were positively correlated with the desaturation index (DI) and the TAC levels were negatively correlated with mean arterial oxygen saturation (SaO_2). Regression analysis results indicated that the TAC levels remained significantly and negatively correlated with mean SaO_2 levels. Moreover, the CRP levels remained significantly correlated with the apnea–hypopnea index and DI after controlling for covariates.
Conclusions: The present study demonstrated that a preferentially adaptive antioxidative response to hypoxia emerges, and the role of OSA with respect to inflammatory reaction is attenuated, in ischemic stroke patients with OSA.

1. Introduction

Obstructive sleep apnea (OSA) is an independent risk factor for ischemic stroke [1]. However, the role of OSA with respect to the mortality and further cardiovascular risk in ischemic stroke patients remains contentious. Sahlin et al. performed a 10-year follow-up study, and indicated that moderate-to-severe OSA in stroke patients is a risk factor of early death, but not for 10-year mortality [2]. Other observational studies suggested that OSA found in stroke patients is a risk factor for stroke recurrence [3,4]. Those studies also associated continuous positive airway pressure (CPAP) nonadherence with a significant increase in new vascular events (especially new ischemic strokes) [5] and a 5-year mortality rate [6]. However, CPAP-noncompliant patients might have problems with general treatment compliance, leading to a more advanced vascular disease [7]. Conversely, Parra et al. performed a randomized controlled trial, which revealed a similar new cardiovascular event and mortality rate at 2-year follow-up between CPAP users and non-users in OSA patients with ischemic stroke [8].

In contrast to the extensive studies on the pathophysiology in middle-aged OSA patients without stroke, oxidative stress and inflammatory reactions due to OSA have seldom been investigated in ischemic stroke patients. Recent studies have reported increased inflammatory biomarkers such as C-reactive protein (CRP) and interleukin 6 (IL-6) in acute ischemic stroke patients with OSA [9–11], which is consistent with the finding in typical middle-aged OSA patients without stroke. Interleukin 6, an atherogenic

* Corresponding author. Department of Physical Medicine and Rehabilitation, Chang Gung Memorial Hospital, No.222, Maijin Rd, Anle District, Keelung City 204, Taiwan. Tel.: +886 2 24329292; fax: +886 2 24313161.
E-mail address: jongyau@cgmh.org.tw (C-Y. Chen).

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marker, increased commensurately in acute ischemic stroke patients with OSA, and was correlated with oxyhemoglobin desaturation and with the desaturation index in ischemic stroke patients with severe OSA [10]. Previous studies found that the inflammatory response markedly changed over time after acute ischemic stroke [12]. According to another study, in subjects with transient pharyngeal muscle alteration, obstructive apneic events significantly improved in the stable stroke phase [13]. Therefore, whether the findings that increased IL-6 and CRP levels found in acute ischemic stroke patients with OSA still hold true in chronic ischemic stroke patients with OSA remains unclear.

As is well known, atherogenesis is linked to oxidative stress and lipid peroxidation [14]. Other studies found that the severity of OSA was negatively correlated with total antioxidant capacity (TAC) [15] and positively correlated with urinary 8-hydroxy-2-deoxyguanosine (8-OHdG) excretion [16]. Oxidative stress markers such as TAC (defined as ferric reducing antioxidant power) were found to be useful in detecting and monitoring redox imbalance and the CPAP therapy effect in OSA patients without stroke [15]. The 8-OHdG is a modified deoxyribonucleic acid (DNA) base that has been used for evaluation of oxidative DNA damage [17]. However, it is believed that OSA patients with ischemic stroke have not been examined.

The present study investigated how the inflammatory status, oxidative stress biomarkers and severity of OSA are related in stable ischemic stroke patients. Portable cardiorespiratory polygraphy is often used in acute stroke patients who are not stable enough to receive full polysomnography (PSG) in a sleep center. However, patients suffering from acute stroke are especially susceptible to anxiety, poor sleep quality, and insomnia – all of which cannot be assessed by these portable systems. Performing a full PSG in the stable phase of ischemic stroke could avoid the possible effects of acute stroke, with respect to the severity of apnea and the main limitation of portable cardiorespiratory polygraphy; this would enable elucidation of the pathophysiologic role of OSA in these patient groups. The present study also evaluated how the severity of OSA and recurrent ischemic stroke are related.

2. Method

2.1. Participants

This prospective study examined consecutive stable ischemic stroke patients who were admitted to the Rehabilitation ward of the teaching hospital. Study participants were diagnosed as having ischemic stroke, based on a full clinical assessment with detailed neurological examinations and neuroimaging studies. Exclusion criteria were: severely decreased consciousness; previous history of intracranial hemorrhage or malignancy; evidence of overt congestive cardiac failure; liver dysfunction with ascites; chronic obstructive pulmonary disease under steroid treatment; advanced renal disease (chronic kidney disease Stage 3 or higher); unstable medical and neurological conditions such as pneumonia, asthma, severe infection or uncontrolled diabetic mellitus (DM); and patients with central sleep apnea (CSA). All participants had similar physical activity, as they received regular physical therapy, occupational therapy, and speech therapy. Drugs or dietary supplements such as vitamins, which might interfere with the inflammatory or oxidative stress, were prohibited; this excluded regular medication prescribed by the physicians for any underlying diseases.

The study protocol received approval from the local ethics committee, and all participants or their next of kin (when the participant's communication was impaired) gave informed consent.

2.2. Clinical evaluation

Upon admission, a comprehensive history was taken, which included demographic data and the prevalence of risk factors for stroke (i.e., smoking, hypertension [HTN], dyslipidemia, DM, cardiac arrhythmia, previous ischemic stroke). Initial stroke severity, as measured by the National Institutes of Health Stroke Scale (NIHSS) [18], was taken from the relevant medical reports. Stroke subtype was classified according to the Trial of Org 10172 in Acute Stroke Treatment criteria [19]. Body mass index, neck circumference, Barthel Index (BI) [20], and Epworth sleepiness scale (ESS) [21], which evaluates the propensity to sleep, were determined on the same day of the PSG examination. The BI was widely used for evaluating functional outcomes in stroke patients.

2.3. Polysomnography

Polysomnography was performed using the Embla N7000 (Somnologica, Iceland) at the sleep laboratory from 22:00 to 05:00. The median time interval between stroke onset and the date of PSG study was 2.2 months (IQR 1.2–4.2). This included: six electroencephalography channels (F3-A1, F4-A2, C3-A1, C4-A2, O1-A1, and O2-A2); an electro-oculogram; a chin and bilateral anterior tibial surface electromyogram; an electrocardiogram; nasal and oral airflow sensors (nasal pressure cannula and oronasal thermistor); thoracic and abdominal movement sensors (inductance plethysmography); and an oxyhemoglobin saturation detector (finger pulse oximetry). A recording time of at least 5 h was required to validate the sleep study. Sleep onset latency, sleep efficiency, and the percentage of total sleep time spent in slow-wave sleep and rapid eye movement (REM) sleep was recorded.

Diagnosis of OSA was based mainly on the American Academy of Sleep Medicine Task Force recommendations [22]. Apnea refers to the cessation of airflow for at least 10 s. The respiratory effort is maintained in obstructive apnea, whereas breathing movements are lacking in central apnea. Mixed apnea refers to the cessation of airflow that is initially associated with the absence of respiratory effort and that persists upon resumption of respiratory effort [22]. Hypopnea refers to a reduction of >50% in airflow for at least 10 s, with either an arousal or oxygen desaturation ≥3%. Oxyhemoglobin desaturation index (DI) (ie, number of desaturations per hour of time in bed) was also calculated. Obstructive sleep apnea was diagnosed when >50% of respiratory events were of obstructive or mixed type. Severe OSA was defined as >30 apnea episodes and/or hypopnea episodes per hour of sleep (apnea–hypopnea index [AHI] > 30 events/h). Central sleep apnea was diagnosed when ≥50% of the respiratory events were of the central type.

2.4. Inflammatory and oxidative biomarkers

Samples of peripheral venous blood and urine were collected after the night that PSG was performed at 05:00. Blood was collected in lithium heparin-containing tubes (4.5 mL lithium heparin PST™ II tubes, BD Vacutainer; BD) and BD Vacutainer SST™ II Advance tubes (Becton Dickinson, Heidelberg, Germany), respectively; they were centrifuged for 10 min at 3000 rpm. Samples were immediately separated into aliquots and stored at –80 °C until analysis in the Medical Center Laboratory of the hospital. Total antioxidant capacity was measured by the ferric reducing ability of plasma assay [23] on the Cobas Mira Plus (Roche Diagnostics, Mannheim, Germany). The intra-assay and inter-assay coefficients of variation were determined to be 2% and 5%; 1% and 3%, respectively, at two levels. Serum CRP was determined by a high-sensitivity assay using a latex aggregation immunoassay (Nanopia CRP, Daiichi Pure Chemicals Co., Ltd.) with a Hitachi 7600-210 analyzer (Hitachi Instruments Engineering Co., Ltd). The method has a lower limit of sensitivity of 0.1 mg/L and inter-assay and intra-assay coefficients of variation of less than 5%. Serum levels of IL-6 were measured with a sandwich enzyme-linked immunosorbent assay (ELISA) by using standard procedures (R&D Systems, Minneapolis, USA). The tests

were quantified at 450 nm in a microplate reader (Spectra MAX 190, Molecular Devices, LLC, California, USA). The intra- and inter-assay coefficients of variation were determined to be 9.2% and 5.7%; 8.8% and 8.0%, respectively, at two levels. The urinary 8-OHdG concentration was determined using a microplate competitive ELISA [24]. The intra-assay and inter-assay coefficients of variation were determined to be 5.9% and 8.0%, respectively. The urinary 8-OHdG excretion was normalized for the urinary creatinine level and was expressed as the urinary (8-OHdG [nanograms/milliliter]/creatinine [milligrams/milliliter]) ratio.

2.5. Statistical analyses

Statistical analyses were performed using statistical software (SPSS version 20, SPSS, Chicago, USA). Normality of data distribution was assessed. Variables not within normal distribution were log-transformed (logCRP, logIL-6 and high-density lipoprotein [logHDL]) to achieve normality, followed by subsequent analysis with parametric tests. Geometric means were then calculated and reported. Participants were stratified into severe and non-severe OSA groups. Noncontinuous variables were compared using a Chi-squared test, and continuous variables were compared using Student's *t*-test (or Mann–Whitney U test for groups without normally distributed data) between the two groups. In the elderly, studies have suggested that the AHI threshold for OSA scoring might be higher than in younger and middle-aged people [25,26]. As OSA in the mild-to-moderate-severity category did not increase cardiovascular morbidity and mortality in long-term outcome studies [27] and CPAP therapy could reduce the excess of nonfatal cardiovascular events in stroke patients with AHI > 20 events/h [5], relationships between the continuous variables in stroke patients with severe OSA were evaluated by Pearson or Spearman correlation analysis, depending on whether or not data were normally distributed. Potential variables were then entered into the multivariate linear regression model to determine the association between OSA severity and target biomarkers. The potential variables were selected if they were related to target biomarkers at $p < 0.10$ or were known to be associated with target biomarkers based on external evidence [16]. Risk factors that are predictive of ischemic stroke recurrence were then identified using logistic regression analysis. Values of $p < 0.05$ were considered to be significant.

3. Results

Twenty-nine women and 63 men with a mean age of 63.4 ± 12.8 years were included in the present study. As is shown in Table 1, participants in the severe OSA group were significantly older ($p = 0.002$), had a significantly higher risk of HTN ($p = 0.021$) and a significantly lower level of logCRP ($p = 0.006$) than those in the non-severe OSA group. There was a trend toward a lower level of logIL-6 in the severe OSA group ($p = 0.085$). Additionally, the two groups did not significantly differ in the levels of TAC and urinary 8-OHdG. All four biomarkers were not significantly correlated with OSA severity (including AHI and DI). The two groups also did not significantly differ in stroke subtypes and severity, the time interval between the onset of stroke and the date of the PSG study, and the prevalence of recurrent stroke (Table 1). As there were no significant differences in stroke subtypes and risk factors (except HTN) between the two groups, the pharmacological treatments of the two groups were comparable. However, there was a trend that more classes of antihypertensive drugs were prescribed for the patients in the severe OSA group (severe OSA 1.40 ± 1.12 vs non-severe OSA 0.97 ± 0.90, $p = 0.063$).

By entering the variables "age," "gender," "body mass index (BMI)," "smoking," "HTN," "DM," "dyslipidemia," "atrial fibrillation," and "severity of OSA" including AHI and DI, respectively, into the equation, logistic regression analysis revealed that only age and smoking were significantly associated with stroke recurrence. Among the subjects with ischemic stroke and severe OSA, the level of TAC was negatively correlated with mean arterial oxygen saturation (SaO_2), and the levels of logCRP, logIL-6, and TAC were positively correlated with DI (Table 2). Multivariate linear regression analysis indicated that TAC values remained significantly and negatively correlated with mean SaO_2 levels after controlling for covariates (i.e., age, gender, BI, ischemic stroke recurrence, DM, HTN, smoking, BMI and total cholesterol level), as shown in Table 3. Moreover, the level of logCRP remained significantly correlated with AHI and DI after adjusting for the same covariates by multivariate linear regression analysis (Table 3); however, the correlation between IL-6 and DI became insignificant after adjustment (Table 3).

Table 1
Epidemiological, clinical variables and laboratory parameters stratified by AHI >/≤ 30/h.

	AHI ≤ 30/h $N = 34$	AHI > 30/h $N = 58$	*p*-value
Age (years)	58.1 (13.9)	66.5 (11.0)	0.002**
Women (*n*)	13 (38.2%)	16 (27.6%)	0.289
Stroke etiology (*n*)			
Large artery	17 (50.0%)	27 (46.6%)	0.749
Cardioembolism	6 (17.6%)	12 (20.7%)	0.723
Lacune	5 (14.7%)	8 (13.8%)	0.903
Other	1 (2.9%)	1(1.7%)	0.699
Undetermined	5 (14.7%)	10 (17.2%)	0.751
Recurrent stroke (*n*)	9 (26.5%)	20 (34.5%)	0.425
BMI (kg/m^2)	24.9 (4.2)	24.9 (3.7)	0.976
Neck circumference (cm)	38.0 (3.4)	38.9 (3.5)	0.277
NIHSS[a] (pt)	11.0 (7.0–16.5)	9.0 (5.0–13.0)	0.237
Barthel index (pt)	36.9 (22.3)	37.5 (21.8)	0.903
ESS (pt)	8.6 (4.2)	9.2 (5.5)	0.553
Interval of PSG[a,c] (months)	1.87 (1.15–3.82)	2.55 (1.40–4.48)	0.295
AHI[a] (events/h)	18.1 (10.3–24.5)	50.9 (38.3–60.9)	0.000**
DI[a] (events/h)	13.1 (7.1–19.1)	46.5 (33.0–59.3)	0.000**
Mean SaO_2 (%)	93.7 (2.2)	92.0 (2.4)	0.001**
Sleep onset latency[a] (min)	18.8 (9.8–34.5)	16.0 (8.0–30.8)	0.409
Sleep efficiency[a] (%)	76.2 (68.6–87.7)	73.2 (62.2–86.1)	0.239
Slow-wave sleep[a] (%)	19.3 (12.2–24.5)	15.6 (6.7–20.8)	0.09
REM sleep[a] (%)	11.8 (5.9–19.5)	9.8 (5.2–17.1)	0.244
Risk factor (*n*)			
Hypertension	25 (74%)	53 (91%)	0.021*
Diabetes	16 (47%)	29 (50%)	0.785
Smoking	14 (41%)	23 (40%)	0.886
Dyslipidemia	27 (79.4%)	42 (72.4%)	0.454
Total cholesterol (mg/dL)	180.9 (44.1)	183.7 (40.9)	0.774
HDL[b] (mg/dL)	36.8	39.1	0.361
LDL (mg/dL)	113.9 (39.0)	109.8 (46.0)	0.686
TAC (μmol/L)	596.3 (118.3)	606.1 (102.6)	0.677
CRP[b] (mg/dL)	2.59	1.50	0.006**
IL-6[b] (pg/mL)	3.84	2.44	0.085
8-ohdg[a] (ng/mgcr)	33.7 (27.2–49.7)	39.5 (29.6–51.5)	0.571

TAC, total antioxidant capacity; CRP, C-reactive protein; IL-6, interleukin-6; 8-ohdg, urinary 8-hydroxy-2-deoxyguanosine; NIHSS, National Institutes of Health Stroke Scale; ESS, Epworth sleepiness scale; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; AHI, apnea–hypopnea index; DI, desaturation index; Mean SaO_2, mean arterial oxygen saturation; REM, rapid eye movement.

* $p < 0.05$; ** $p < 0.01$. Values are means (SD), unless indicated otherwise.

[a] Medium (IQR).

[b] Geometric mean.

[c] Time interval from stroke onset to the date of PSG study.

4. Discussion

It is believed that the present study demonstrates, for the first time, that the severity of OSA is positively associated with the TAC and CRP in ischemic stroke subjects with severe OSA, even after adjusting for common covariates. Along with the findings that severe OSA is not independently associated with recurrent ischemic stroke and the CRP level of the severe OSA group is significantly lower than

Table 2
Correlations between baseline data and biomarker in subjects with severe OSA.

	TAC		LogIL-6		LogCRP		8-OHdG	
	Pearson's *r*	*p*-value	Pearson's *r*	*p*-value	Pearson's *r*	*p*-value	Pearson's *r*	*p*-value
TAC			0.199	0.253	0.096	0.495	0.041	0.757
LogIL-6	0.199	0.253			0.239	0.188	–0.085	0.626
LogCRP	0.096	0.495	0.239	0.188			0.114	0.414
8-OHdG	0.041	0.757	–0.085	0.626	0.114	0.414		
Age	–0.006	0.962	0.260	0.131	0.267	0.053	0.116	0.387
NIHSS	–0.136[a]	0.385	0.113[a]	0.575	–0.040[a]	0.810	0.065[a]	0.678
Barthel index	0.052	0.697	–0.277	0.108	–0.128	0.362	–0.011	0.937
BMI	0.451	0.000**	–0.237	0.177	–0.004	0.979	–0.076	0.573
Neck circ.	0.229	0.086	0.076	0.669	0.085	0.548	–0.270	0.042*
Total cholesterol	0.288	0.038*	0.144	0.441	–0.048	0.750	–0.199	0.156
HDL	–0.187	0.184	0.163	0.380	0.284	0.053	0.104	0.463
LDL	0.213	0.129	0.202	0.276	–0.012	0.938	–0.132	0.350
AHI	0.253	0.055	0.141	0.421	0.451	0.001**	0.116	0.387
DI	0.313	0.017*	0.342	0.045*	0.466	0.000**	0.214	0.107
Mean SaO_2	–0.395	0.002**	0.110	0.530	–0.150	0.285	–0.091	0.498

TAC, total antioxidant capacity; CRP, C-reactive protein; IL-6, interleukin-6; 8-OHdG, urinary 8-hydroxy-2-deoxyguanosine; NIHSS, National Institutes of Health Stroke Scale; BMI, body mass index; Neck circ., neck circumference; HDL, high-density lipoprotein; LDL, low-density lipoprotein; AHI, apnea–hypopnea index; DI, desaturation index; OSA, obstructive sleep apnea; SaO2; arterial oxygen saturation.
* $p < 0.05$; ** $p < 0.01$.
[a] Spearman's ρ.

that of the non-severe OSA group, the results suggest that a preferentially adaptive antioxidative response to hypoxia emerges and the role of OSA, with respect to inflammatory reaction, is attenuated in ischemic stroke patients with OSA.

The negative correlation between TAC and mean SaO_2 remains statistically significant after adjusting for age, gender, stroke outcome, stroke recurrence, DM, HTN, smoking, BMI, and total cholesterol level. The higher degree of hypoxia that the patients experience during sleep implies a greater ferric reducing antioxidant power, which the subjects had. These adaptive responses to hypoxia contradict previous findings in which TAC was decreased in middle-aged subjects with severe OSA [15], but support the hypothesis of ischemic preconditioning resulting from the nocturnal cycles of hypoxia–reoxygenation [28]. Ischemic preconditioning was mostly found in the heart [29,30] but was identified to occur in the brain as well [31,32]. Carotid atherosclerosis has been found to be independently associated with OSA in middle-aged individuals [33]. However, Sforza et al. found that the incidence of carotid atherosclerosis was not associated with OSA in healthy elderly subjects and concurred with the notion that the elderly are protected from the cardiovascular consequences of OSA [34]. For individuals younger than 70 years old, time with SaO_2 <90% was found to be a significant predictor of mortality in the Sleep Heart Health Study [35]. However, Lavie et al. unexpectedly found an advantage of sleep apnea in terms of the risk of dying in patients older than 70 years [36]. These authors also speculated that sleep apnea patients older than 70 years may constitute an exceptionally resistant group of survivors whose cardiovascular system is exceptionally adapted to the prolonged stress associated with the syndrome [36]. As the mean age of the severe OSA group in the present study was 66.5 years, the finding that the level of mean SaO_2 is negatively correlated with TAC might be a biologically plausible mechanism to explain why the SaO_2 level fails to predict mortality in the elderly with OSA.

Dziewas et al. noted that sleep apnea is independently associated with raised levels of CRP in acute ischemic stroke patients [11]. In contrast to the subjects in their study, the subjects in the present study were in the subacute-to-chronic phase of ischemic stroke, suffered from relatively more severe stroke (medium NIHSS 9–11 in the present study and mean NIHSS 4.3–6.4 in their study), and had a higher level of CRP (geometric mean CRP 1.50–2.59 in the present study vs mean CRP 0.37–1.55 in their study). Despite the findings in the present study that the level of CRP is significantly correlated with AHI and DI in stroke patients with severe OSA, the result showing the CRP level of the severe OSA group to be significantly lower than that of the non-severe OSA group argues against the findings of Dziewas et al. [11]. On the contrary, the decreased CRP and IL-6 level of the severe OSA group corroborate the hypothesis of ischemic preconditioning [28]. The nuclear factor kappa B (NF-κB) pathway, the primary pathway for the systemic inflammation in patients with OSA, could be activated by reactive oxygen species (ROS) [37]. Although levels of TAC and CRP were both significantly correlated with OSA severity in the severe OSA group, it is speculated that the adaptive antioxidative capacity might overwhelmingly outweigh the proinflammatory effect of OSA as the severity of OSA increased. In contrast, inflammatory status was not mainly determined by OSA and would not be largely affected by the antioxidative capacity of the non-severe OSA group. Accordingly, the adaptive antioxidative capacity of patients with severe OSA might

Table 3
Associations between parameters of PSG and biomarkers after adjusting for age, BMI, gender, Barthel index, stroke recurrence, smoking, DM, HTN and total cholesterol in subjects with severe OSA.

PSG parameters	TAC		LogCRP		LogIL-6		8-OHdG	
	β	*p*-value	β	*p*-value	β	*p*-value	β	*p*-value
AHI	0.071	0.627	0.442	0.006**	–0.021	0.929	0.064	0.701
DI	0.182	0.193	0.461	0.002**	0.226	0.359	0.220	0.166
Mean SaO_2	–0.323	0.020*	–0.045	0.783	0.155	0.497	–0.082	0.613

β: Standardized Regression Coefficient.
OSA, obstructive sleep apnea; TAC, total antioxidant capacity; CRP, C-reactive protein; IL-6, interleukin-6; 8-OHdG, urinary 8-hydroxy-2-deoxyguanosine; AHI, apnea–hypopnea index; DI, desaturation index; PSG, polysomnography; BMI, body mass index; DM, diabetic mellitus; HTN, hypertension; SaO2; arterial oxygen saturation.
* $p < 0.05$; ** $p < 0.01$.

neutralize the toxicity of ROS; therefore, it dampened the baseline level and the rising rate of inflammatory reaction caused by intermittent hypoxia and could be the plausible mechanism for the decreased CRP and IL-6 level, as compared to that of the non-severe OSA group. The present results also suggest that the relationship between the CRP level and the OSA severity might change gradually after the onset of stroke. Exactly whether the thresholds for diagnosing and treating OSA differ in individuals with cardiovascular disease from those who are otherwise healthy remains unclear [38]. A recent systemic review study recommended identifying the predictive ability of various AHI threshold values [39]. The present results suggest that the extent to which OSA affects the level of CRP becomes significant only when the AHI threshold is set to 30 events/h in ischemic stroke patients. The observed weak, albeit statistically significant, univariate correlation between IL-6 and DI found in the severe OSA group adds some weight to the suggestion that the AHI threshold should be set to 30 events/h with respect to the inflammatory reaction due to OSA.

The finding that severe OSA is not independently associated with stroke recurrence contradicts previous studies in which acute stroke patients were examined using a portable system [3,4]. Rola et al. [4] studied 72 subjects after mild ischemic stroke or transient ischemic attack, and concluded that sleep-disordered breathing (SDB) significantly increased the incidence of recurrent stroke in a 2-year follow-up. In their study, SBD was not further classified into an obstructive or central type. Previous studies have also demonstrated that the prevalence of CSA is higher in the acute phase of stroke, with a tendency to decrease in the chronic phase [40]. Therefore, attributing the increased incidence of recurrent stroke found in their study to the OSA alone would be inappropriate. Dziewas et al. [3] prospectively studied 102 acute stroke patients, and indicated that SDB is an independent risk factor for stroke recurrence. However, their study had two major limitations: the forward stepwise logistic regression analysis and that SDB was evaluated simultaneously with the nasal oxygen supply. Biologists are advised to refrain from applying stepwise model selection methods [41]. As age is an independent predictor of severe OSA in stroke patients [42], logistic regression analysis using forward stepwise or entering methods might yield different results. In this study, AHI was independently associated with stroke recurrence by the forward stepwise method. However, AHI failed to maintain the independent association for stroke recurrence after forcefully entering “age” into the equation. The second limitation was that SDB was evaluated simultaneously with the nasal oxygen supply. Exactly how oxygen supply affects the severity of OSA in acute stroke patients remains unclear, which possibly biased the final results.

Despite its contributions, the present study also had certain limitations. While only recruiting subjects in need of inpatient rehabilitation, the present study excluded subjects with minor stroke, who received out-patient rehabilitation, and severe stroke patients who died in the acute phase or could not follow orders clearly enough to receive in-patient rehabilitation. Therefore, an extrapolation of the results to other patients is impossible. Moreover, the mechanisms of the adaptive responses found in the study remain speculative.

Despite the above limitations, the present study demonstrated that the effects of OSA on inflammation become obvious only in ischemic stroke patients with severe OSA and may be clinically irrelevant due to the complex comorbidities and the accompanied adaptive antioxidative response to hypoxia. Future studies on the autonomic function, atherosclerosis, and arterial stiffness are recommended to elucidate how OSA affects ischemic stroke patients, because a higher prevalence of hypertension is observed in severe OSA patients. As the compliance with CPAP in stroke patients with OSA is a challenging issue, aggressive blood pressure control appears to be the most important strategy in treating these patients.

Conflict of interest

The authors declare that they have no conflicts of interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.07.027.

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